In re Application of: Gera NEUFELD
Serial No.: 10/539,289
Filed: June 16, 2005
Office Action Mailing Date: January 23, 2008

Examiner: Zachary C. HOWARD
Group Art Unit: 1646
Attorney Docket: 29432

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-23 are in this Application. Claims 4-23 have been withdrawn from consideration. Claims 1-3 have been rejected under 35 U.S.C. *§* 112. Claims 1-3 have been rejected under 35 U.S.C. *§* 102. Claims 1-3 have been rejected under 35 U.S.C. § 103. Claims 2 and 3 have been canceled herewith. Claim 1 has been amended herewith.

Amendments To The Claims

35 U.S.C. § 112, 2nd paragraph Rejection

The Examiner has rejected claims 1-3 under 35 USC §112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner asserts that the phrases "devoid of a VEGFR-1 binding activity" in claim 1 and "set forth by" in claim 2 are unclear. Examiner's rejections are respectfully traversed.

In order to expedite prosecution of this case, Applicant has elected to amend claim 1 to recite:

> *"An isolated $VEGF_{145}$ polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:4"*
> (Emphasis added)

to thereby overcome Examiner's rejections.

Claims 2 and 3 have been cancelled, thereby rendering moot Examiner's rejections.

35 U.S.C. § 112, 1st paragraph Rejection

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The Examiner has rejected claims 1-3 under 35 USC §112, 1st paragraph because the specification, while being enabling for a polypeptide of SEQ ID NO:4, does not reasonably provide enablement for an isolated $VEGF_{145}$ polypeptide devoid of a VEGFR-1 binding activity. The Examiner states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Examiner's rejections are respectfully traversed.

Applicant points out that currently amended claim 1 renders moot Examiner's enablement rejections.

The Examiner has rejected claims 1-3 under 35 USC §112, 1st paragraph as failing to comply with the written description requirement. The Examiner states that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states that it is clear that Applicant has possession of an isolated polypeptide of SEQ ID NO:4 but the specification fails to describe or teach any other polypeptide which differs from the sequence of SEQ ID NO:4 and retains the recited characteristics of "devoid of a VEGF-R binding activity" and the necessary functional activity of "capable of binding to VEGFR-2". Examiner's rejections are respectfully traversed.

Applicant points out that currently amended claim 1 renders moot Examiner's written description rejections.

In view of the above claim amendments and remarks Applicant believes to have overcome the 35 U.S.C. § 112 rejections.

35 U.S.C. § 102 Rejections

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The Examiner has rejected claims 1-3 under 35 USC § 102(b) as being anticipated by Li et al., 2000 (J. Biochemical Chemistry, 275: 29823-29828).

Specifically, the Examiner states that Li et al., teach a VEGF polypeptide with a reduced binding to VEGFR-1 due to a single mutation of residue 63 or 66, but with a binding to VEGFR-2 that is equivalent to the non-mutated form; and another variant with a triple mutation of Asp63-Ser, Gly-65-Met and Leu-66-Arg (KDR-sel2) which as compared to wild-type $VEGF_{145}$ includes a truncation of residues 110-145, and since as indicated above with respect to 35 U.S.C. 112, 2nd paragraph rejections, the phrase "devoid of VEGFR-1 binding activity" in claim 1 has been interpreted broadly to encompass any polypeptide that has less than full VEGFR-1 binding activity, and the phrase "as set forth by SEQ ID NO:4" has been interpreted to encompass variants of SEQ ID NO:4 with one or more mutations, the polypeptides taught by Li et al., anticipate claims 1-3. Examiner's rejections are respectfully traversed.

Applicant points out that, since the art of Li et al. fail to describe the polypeptide claimed in currently amended claim 1, the novelty rejection under 35 USC § 102(b) should be withdrawn.

The Examiner has further rejected claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Cunningham et al. (WO 00/63380). Specifically, the Examiner states that Cunningham et al. teach a mutant $VEGF_{109}$ polypeptide (LK-VRB-2s) and a mutant $VEGF_{165}$ sequence (LK-VRB-2f), each with three point mutations: Arg-63-Ser, Gly-64-Met and Leu-66-Arg which can bind VEGFR-2 but have reduced VEGFR-1 binding activity. Examiner's rejections are respectfully traversed.

Applicant points out that, since the art of Cunningham et al. fail to describe the polypeptide claimed in currently amended claim 1, the novelty rejection under 35 USC § 102(b) should be withdrawn.

In view of the above claim amendments, arguments and remarks Applicant believes to have overcome the 35 U.S.C. § 102(b) rejections.

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35 U.S.C. § 103 Rejections

The Examiner has rejected claims 1-3 under 35 USC § 103(a) as being unpatentable over Cunningham (WO 00/63380) in view of Poltorak et al., 1997 (J. Biological Chemistry 272:7151-7158). Specifically, the Examiner states that this rejection pertains to a specific embodiment of an isolated $VEGF_{145}$ polypeptide with the amino acid sequence of SEQ ID NO:4, and that it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make the amino acid sequence of SEQ ID NO:4 by making the mutations taught by Cunningham (to residues 63, 65 and 66) in the $VEGF_{145}$ sequence taught by Poltorak; and that the person of ordinary skill in that art would be motivated to do so because (1) $VEGF_{145}$ meets the definitions of a "processed" or "deleted" VEGF variant as suggested for use by Cunningham as part of the KDR-selective VEGF of the invention and (2) in the absence of other evidence, the mutated $VEGF_{145}$ sequence could used for endothelial cell proliferation as well as the mutated $VEGF_{165}$ taught by Cunningham; and a person of ordinary skill in the art would have had a reasonable expectation of success because producing mutated proteins is routine in the art. Examiner's rejections are respectfully traversed.

Applicant points out that in sharp contrast to Examiner's assertion the wild type $VEGF_{145}$ polypeptide includes additional sequences (exon 6a; see Figure 1A, Page 7153 in Poltorak et al.) as compared to the wild type $VEGF_{165}$ polypeptide and thereby does not meet the definition of a "processed" or "deleted" form of $VEGF_{165}$.

In addition, as shown in Poltorak et al., Page 7153, Figure 1A and in the below $VEGF_{145}$ and $VEGF_{165}$ sequences, while wild-type $VEGF_{145}$ includes exon 6a (**bolded** letters in the below $VEGF_{145}$ sequence) but lacks exon 7, wild-type $VEGF_{165}$ lacks exon 6a but includes exon 7 (**bolded** letters in the below $VEGF_{165}$ sequence) and therefore the $VEGF_{165}$ polypeptide includes seven additional cystein residues [See underlined and bolded cystein ("**C**") residues in the below sequences] which are absent in the $VEGF_{145}$ polypeptide.

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$VEGF_{165}$ [amino acids 27-191 of GenBank Accession No. AAM03108, a total of 16 cystein residues)

APMAEGGGQNHHEVVKFMDVYQRSYCHPIETLVDIFQEYPDEIEYIFKPSCVP
LMRCGGCCNDEGLECVPTEESNITMQIMRIKPHQGQHIGEMSFLQHNKCECRP
KKDRARQEN***PCGPCSERRKHLFVQDPQTCKCSCKNTDSRCKARQLELNERTC***
RCDKPRR

$VEGF_{145}$ (amino acids 1-145 of SEQ ID NO:3 in the instant application; a total of 9 cystein residues)

APMAEGGGQNHHEVVKFMDVYQRSYCHPIETLVDIFQEYPDEIEYIFKPSCVP
LMRCGGCCNDEGLECVPTEESNITMQIMRIKPHQGQHIGEMSFLQHNKCECRP
KKDRARQEKKSV***RGKGKGQKRKRKKSRYKSWSV***CDKPRR

As is well known to those of ordinary skills in the art, since cystein residues can form intra or inter di-sulfide (S-S) bonds in the mature protein, presence or absence of such residues can directly affect the protein secondary and tertiary structure.

Thus, it is Applicant's position that a person of ordinary skills in the art would not have had a reasonable expectation of success because the mutations disclosed in Cunningham et al., were introduced to proteins having different secondary and tertiary structures than the protein of the claimed invention.

Taken together, it is Applicant's position that the mutated $VEGF_{145}$ polypeptide as now claimed is novel and non-obvious over the art of Cunningham and Poltorak, either alone or in combination. Withdrawal of the 103(a) rejections is respectfully requested.

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In view of the above amendments and remarks it is respectfully submitted that claim 1 is now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Martin D. Moynihan
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Date: July 23, 2008

Enclosed:

- Petition for Extension (three months)